REMARKS

Claims 1-5, 7, 9-18, and 21-25 are pending in the application. Claim 19 has been canceled without prejudice or disclaimer. Claims 1, 10, and 13-16 have been amended. Support for the amendments to claims 1 and 10 can be found in the specification, e.g., at page 6, first full paragraph. Support for the amendments to claims 13-16 can be found in the specification, e.g., at page 8, third full paragraph.

Drawings

The Examiner objected to the drawings originally filed on May 25, 2001. Office Action Summary at box 10. Applicants enclose a set of replacement drawings (3 sheets of Figures 1-3) and request that the originally-filed drawings be replaced with those replacement drawings. The replacement drawings are simply better copies of the originally-filed drawings and add no new matter.

Priority

The Examiner alleged that "[a]pplicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5))." Action at page 2.

Applicants have not claimed priority to a domestic application under 35 U.S.C. § 120. Rather, applicants claimed priority under 35 U.S.C. § 119 to Japanese Patent

Application No. 2001-140538, filed May 10, 2001. A Claim for Priority; Declaration, Power of Attorney and Petition citing the priority application; and a certified copy of the priority application were filed at the U.S. Patent and Trademark Office on August 17, 2001. Applicants note that the Examiner acknowledged the claim for priority on the current Office Action Summary at box 13.

Applicants respectfully request that the Examiner notify them if she believes that priority has not been properly claimed to Japanese Patent Application No. 2001-140538, and that the Examiner indicate what specific deficiencies are alleged.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Action at page 3. Specifically, the Examiner alleged that

> the specification, while being enabling for producing a rodent bone metastasis model animal by intravenous administration of human lung small cell carcinoma cell line SBC-5 cells, wherein the rodent is immunodeficient, does not reasonably provide enablement for producing a rodent bone metastasis model animal by intramuscle, intracutaneous, subcutaneous, and intraperitoneal administration of any cancer or tumor cells that highly express PTHrP.

Id.

Claim 1 has been amended to recite

> 1. A rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, wherein a single cell suspension of human tumor cells that induce bone metastasis and highly express PTHrP has been introduced by intravenous administration, wherein the animal is immunodeficient, and wherein the metastasis occurs in the animal's own bone.

Claims 2-4, 7, 9, 24, and 25 ultimately depend from claim 1. Claim 10 has been amended to recite

> 10. (Currently amended) A method for producing a rodent exhibiting bone metastasis of tumor cells, comprising:
> (i) providing an immunodeficient rodent; and
> (ii) introducing a single cell suspension of human tumor cells that induce bone metastasis and highly express PTHrP into the animal by intravenous administration, wherein the metastasis occurs in the animal's own bone.

Claims 11-18 and 21-23 ultimately depend from claim 10. Claim 19 has been canceled without prejudice or disclaimer.

First, the Examiner stated that the rejection to immunodeficient rodent is withdrawn with respect to all of the claims, except "claims 13-16 [which] are drawn to a rodent with reduced immunity rather than immune deficient, thus, the rejection remains applicable to these claims." Action at page 3 (emphasis in original).

Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claims 13-16 to recite an "immunodeficient rodent" rather than a "rodent having reduced immunity."

Second, the Examiner alleged that "the specification fails to teach the causative relationship of PTHrP and bone metastasis for any tumor cell that expresses high levels of PTHrP. In fact, quite a few prior art of record have concluded that PTHrP expression is not necessary or correlated with bone metastasis." Action at page 4. The Examiner cited Guise et al. (1994) *J. Bone Min Res*, 9: S128 ("Guise") as allegedly disclosing that "increased PTHrP could enhance osteolytic metastases, but low PTHrP breast cancer cells could exhibit bone metastasis as well." *Id.* However, this citation does not bear the weight the Examiner gives it. The enablement of claims is not disproved simply because there are alternative ways of reaching a similar result. The enablement of

claims 1-5, 7, 9-18, and 21-25 does not require that no *other* cells be capable of metastasizing to bone. Indeed, Guise demonstrates that cells expressing PTHrP do metastasize to bone ("Mice inoculated in the left ventricle with the high-expressing clone, MDA/PTHrP-1, had an average of 16.3 +/- 3.8 osteolytic bone lesions radiographically at 3 weeks. . . .").

The Examiner also cited Rabbani et al. (1999) *Int. J. Cancer*, 80: 257-64 ("Rabbani"), alleging that "[I]t appears that the skeletal invasiveness is more relevant to the route of administration rather than the levels of PTHrP"; and Blomme et al. (1999) *The Prostate*, 39: 187-197 ("Blomme"), alleging that "PTHrP overexpression by MATLyLu cells was not associated with any difference in the incidence of bone metastasis, size of metastatic foci or tumor-cell proliferation." *Id.*

Both Rabbani and Blomme discuss bone metastasis by the same prostate tumor cell line, MATLyLu. In both cases, the researchers found that MATLyLu cells are already capable of metastasizing to bone and that over-expression of PTHrP in those cells does not *further increase* bone metastasis. As above, the enablement of claims 1-5, 7, 9-18, and 21-25 is not disproved simply because *other* cells are capable of metastasizing to bone. Indeed, another document cited by the Examiner supports this position entirely. Specifically, Lelekakis et al. (1999) *Clin. & Exp. Metast.*, 17: 163-170 ("Lelekakis"), recognizes that "evidence for the role of PTHrP in the establishment of breast tumours in bone is convincing," but that "it remains to be established whether other bone resorbing factors may be produced by the tumours to provide alternative or complementary mechanisms." Lelekakis at page 169, right column. In fact, in each of the documents cited by the Examiner, cells that over-express PTHrP are shown to

metastasize to bone. Thus, contrary to the Examiner's contention, there is a clear correlation between expression of PTHrP and bone metastasis in the documents cited by the Examiner. Indeed, Lelekakis specifically notes that correlation in the abstract, stating that "secretion of parathyroid hormone-related protein [PTHrP], a role for which has been implicated in breast cancer spread to bone, correlates with metastasis to bone." Lelekakis at Abstract.

Applicants assert that claims 1-5, 7, 9-18, and 21-25 are therefore enabled and that the documents cited by the Examiner only support the finding that one skilled in the art could make and use the claimed invention as of the filing date of the application.

Third, the Examiner alleged that "[w]ith respect to routes of administration, the specification only illustrates bone metastasis of human lung small cell carcinoma cell line SBC-5 cells via intravenous administration, whereas claims encompass intramuscular, intracutaneous, subcutaneous, and intraperitoneal administration." Action at page 5. Specifically, the Examiner cited a number of documents that allegedly disclose that certain routes of administration are less likely to result in bone metastases.

Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claims 1 and 10, as shown above, to recite "intravenous administration."

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-5, 7, 9-18, and 21-25 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Action at page 6. Specifically, the Examiner alleged that the "[t]he specification fails to define what levels of expression is considered 'high', thus, the metes and bounds of the claims are unclear." *Id.*

Applicants respectfully traverse. Claims 1 and 10 are shown above. Claims 2-5, 7, 9, 24, and 25 ultimately depend from claim 1 and claims 11-18 and 21-23 ultimately depend from claim 10. Claim 19 has been canceled without prejudice or disclaimer.

Applicants assert that the specification clearly and expressly defines the term "highly expressing", e.g., at pages 6 and 7, where it states that "[t]he term 'highly expressing' means herein that PTHrP can be detected at a certain concentration or higher in cell culture supernatant, in particular, in the case of measuring PTHrP C-terminus, that PTHrP can be detected in the concentration higher than that detected in normal individuals." The specification also states that "the cases where 1.1 pmol/L or higher PTHrP is detected in measuring PTHrP-N terminus (for example, Mitsubishi kagaku Bio-chemical Laboratory Inc.), and where 55.3 pmol/L or higher PTHrP is detected in measuring PTHrP-C terminus (for example, SRI, Inc.) are included in the situation." Thus, applicants assert that the metes and bounds of the term "highly expressing" are clear to one skilled in the art in view of the definition provided in the specification.

The Examiner alleged that the "[c]laims are vague and indefinite because of claim recitation, 'in which' (line 2 of claims 1), it is unclear what 'which' refers to, e.g.

bone, tumor cells or the animal, and thus the metes and bounds of the claims are unclear." Action at page 7.

Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 1 to recite "wherein" in place of "in which" to even more clearly recite that the single cell suspension has been introduced into the rodent.

The Examiner alleged that "[c]laims are vague and indefinite because of claim recitation, 'tumor cells that induce bone metastasis' (claims 1, 10). It appears that the tumor cells would develop bone metastasis rather than induce bone metastasis." *Id.*

Applicants respectfully traverse. Applicants assert that the term "induce" does not render the claims "vague and indefinite." The Manual of Patent Examining Procedure clearly states that "[t]he Examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." MPEP § 2173.02 (emphasis added). Furthermore, the Examiner "should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirements." *Id.* Thus, the term "induced" meets the threshold requirements of clarity and precision, and one skilled in the art would understand the metes and bounds of the claim as written.

Finally, the Examiner alleged that "[c]laims 13, 14, 15, and 16 recite the limitation, 'the step of providing a rodent having reduced immunity'. There is insufficient antecedent basis for this limitation in the claims." Action at page 7.

Solely to expedite prosecution and without acquiescing to the rejection, claims 13-16 have been amended, as discussed above, to recite an "immunodeficient rodent" rather than a "rodent having reduced immunity."

Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-5, 7, 9-18, and 21-25 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 103

The Examiner rejected claims 1, 2, 4, 5, 7, 10, 11, 19, 21, 24, and 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lelekakis. Action at page 8. Specifically, the Examiner alleged that "*Lelekakis et al* teach a mouse model of bone metastasis, wherein a single cell suspension of spontaneous arising mammary carcinoma cell line 4T1.2 was introduced to female Balb/c mice by intravenous (lateral tail vein) and mammary fat pad injection, wherein by day 20 post-injection, the metastases were observed in the animals' own lung and vertebrae bone, wherein the cells highly express PTHrP. *Id.* (Citations omitted.) The Examiner further alleged that "*Lelekakis et al* do not use an immunodeficient animal, but reviewed the art-known bone metastatic animal model for studying breast cancer in immunodeficient mice, and teach of the advantage of their model is closely resemble the naturally occurring metastatic breast cancer." *Id.* (Citations omitted.)

Applicants respectfully traverse. Claims 1 and 10 are shown above. Claims 2, 4, 5, 7, 24, and 25 ultimately depend from claim 1. Claims 11 and 21 ultimately depend from claim 10. Applicants have canceled claim 19 without prejudice or disclaimer.

Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claims 1 and 10 to recite "a single cell suspension of human tumor cells." Lelekakis discusses only injection of mouse tumor cells. Moreover, Lelekakis does not teach or suggest the use of human tumor cells in their breast cancer metastasis model.

Furthemore, in discussing the prior use of immunodeficient mice, Lelekakis notes the disadvantages of those models, which "are dependent upon the injection of tumor cells into the left ventricle of the heart in order to promote tumour cell delivery to bone and therefore can only evaluate factors important for invasion of bone and interaction of tumor cells with the bone environment." Lelekakis at pages 163-164. Thus, applicants assert that Lelakakis teaches away from the claimed invention, which recites the use of immunodeficient rodents.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 4, 5, 7, 10, 11, 19, 21, 24, and 25 under 35 U.S.C. § 103 over Lelekakis.

Applicants respectfully assert that claims 1-5, 7, 9-18, and 21-25 are in condition for allowance and request that the Examiner issue a timely Notice of Allowance. If the Examiner does not find the claims to be allowable, the undersigned requests that the Examiner call her at (650) 849-6656 to set up an interview.

Please grant any extensions of time required to enter this Amendment and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

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